International Federation of Gynecology and Obstetrics

FIGO

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OF
GYNECOLOGY & OBSTETRICS

HPV VACCINATION

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Cervical cancer is a rare

long-term outcome of persistent infection with

one or more

of high-risk HPV types

(16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82)

With these interventions, elimination of cervical cancer can be possible!

- Socio-economic development
- Women's awareness / empowerment
- HPV vaccination
- Screening
- Early diagnosis and treatment

Characteristics of HPV vaccines

	Gardasil ® (Quadrivalent vaccine)	**Cervarix ®** (Bivalent vaccine)
Manufacturer	Merck	GSK
VLP types	6/11/16/18	16/18
Dose L1 protein	20/40/40/20 µg	20/20 µg
Producer cells	Saccharomyces cerevisiae expressing L1	Trichoplusia ni (Hi 5) insect cell line infected with L1 recombinant baculovirus
Adjuvant	225 µg Aluminum hydroxyphosphate sulfate	500 µg aluminum hydrxyde, 50 µg 3-O-deacylated-4'-monophosphoryl lipid A
Schedule	0, 2, 6 months	0, 1, 6 months

Global Phase III efficacy trials with disease endpoints

Quadrivalent vaccine

(Gardasil™, Merck Co.)

- HPV 6/11/16/18 vaccine vs. placebo (0, 2, 6 mo)
- Age range 16-26
- N=17,622
- Study start: 2002
- 4-year follow-up
- FUTURE I/II (Protocols 013, 015)

Europe, Asia-Pacific, Latin America, North America (13 countries)*

Bivalent vaccine

(Cervarix™, GlaxoSmithKline)

- HPV 16/18 vaccine vs. Havrix (0, 1, 6 mo)
- Age range 15-25
- N= 18,644
- Study start: 2004
- 4-year follow-up
- PATRICIA (HPV-008)

Europe, Asia-Pacific, Latin America, North America (14 countries)*

***Predominantly Northern Europe**

Courtesy: Dr Paavonen

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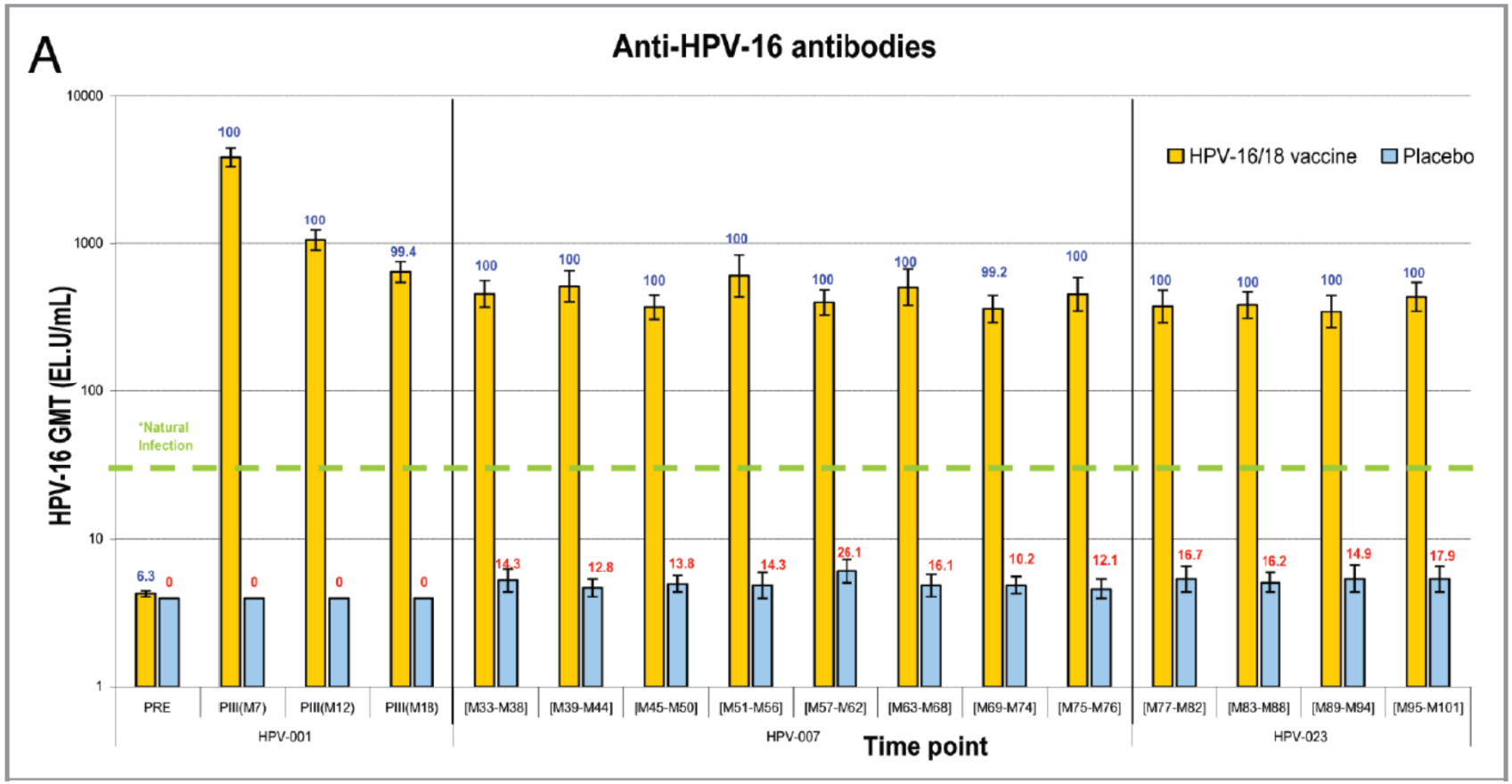
Immunogenicity of the bivalent vaccine up to 8.4 y after vaccination: seropositivity rates and geometric mean titers for *HPV 16*



Roteli-Martins CM *et al*, Hum Vaccin Immunother. 2012;8(3):390-7

FIGO
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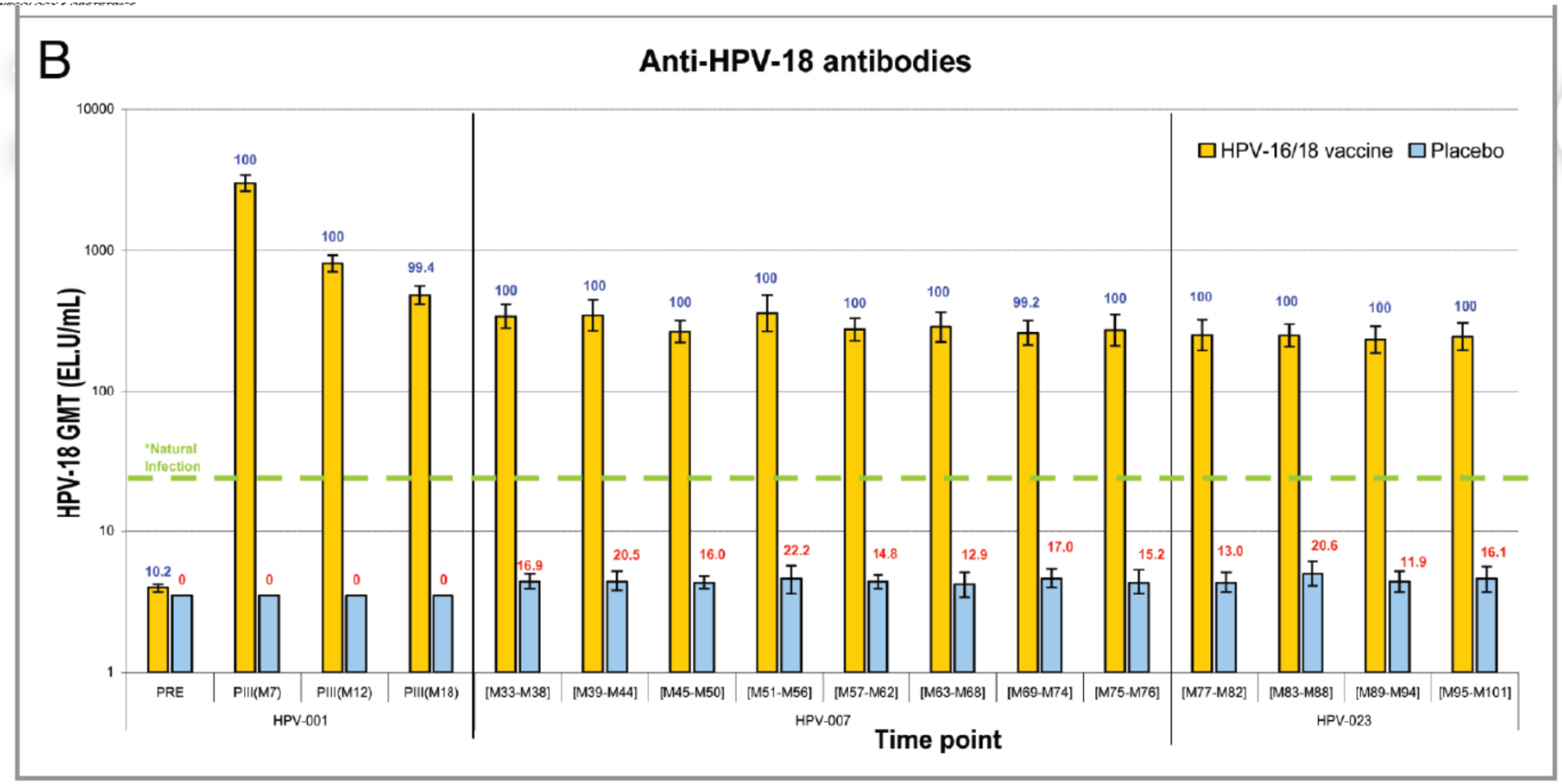
Immunogenicity of the bivalent vaccine up to 8.4 y after vaccination: seropositivity rates and geometric mean titers for *HPV 18*



Roteli-Martins CM *et al*, Hum Vaccin Immunother. 2012;8(3):390-7

FIGO
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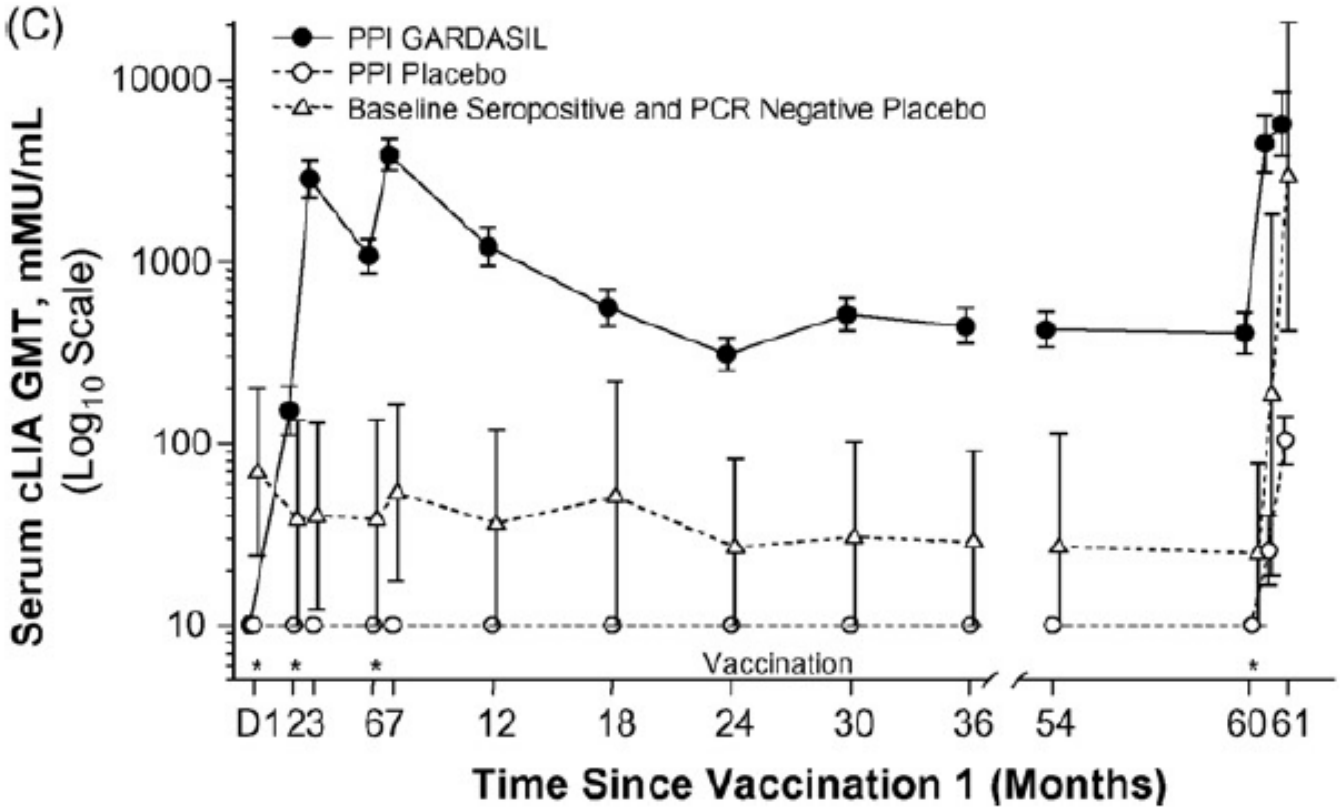
Persistence of *anti-HPV16* response following three-doses of quadrivalent vaccine or placebo and booster



Olsson SE *et al*, Vaccine. 2007;25(26):4931-9

FIGO
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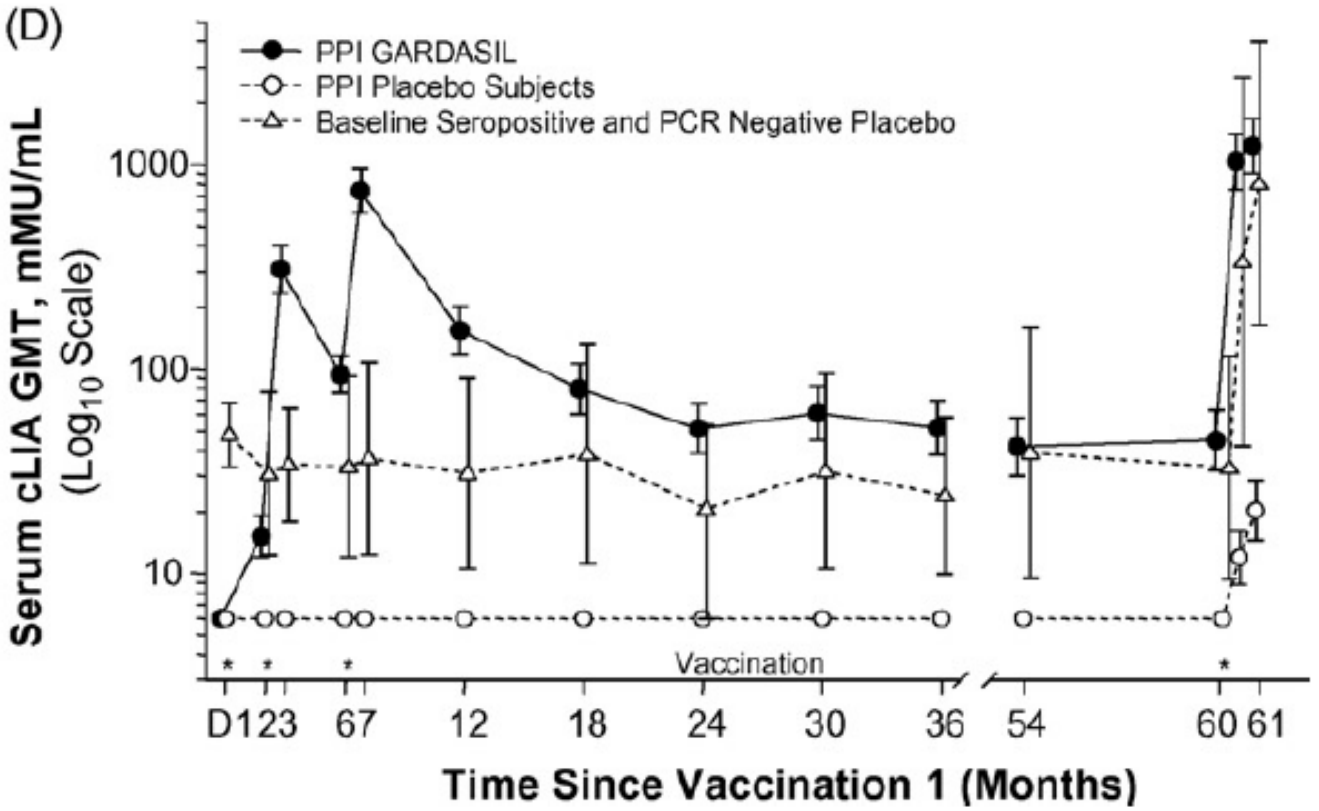
Persistence of *anti-HPV18* response following three-dose of quadrivalent vaccine or placebo and booster



Olsson SE *et al*, Vaccine. 2007;25(26):4931-9

Per-protocol efficacy for prevention of HPV-type disease outcomes among females in trials of the bivalent and quadrivalent HPV vaccines, end-of-study analyses

Vaccine/Endpoint related type	Vaccine		Control		Vaccine efficacy
	No.	Cases	No.	Cases	%
Quadrivalent vaccine					
CIN2/3 or AIS					
HPV 6, 11, 16, 18	7,864	2	7,865	110	98.2
HPV 16	6,647	2	6,455	81	97.6
HPV 18	7,382	0	7,316	29	100.0
VIN/VaIN2/3					
HPV 6, 11, 16, 18	7,900	0	7,902	23	100.0
HPV 16	6,654	0	6,467	17	100.0
HPV 18	7,414	0	7,343	2	100.0
Genital warts					
HPV 6 and/or 11	6,718	2	6,647	186	98.9
Bivalent vaccine					
CIN2/3 or AIS					
HPV 16 and/or 18	7,338	5	7,305	97	94.9
HPV 16	6,296	2	6,160	81	97.6
HPV 18	6,789	3	6,739	23	87.1

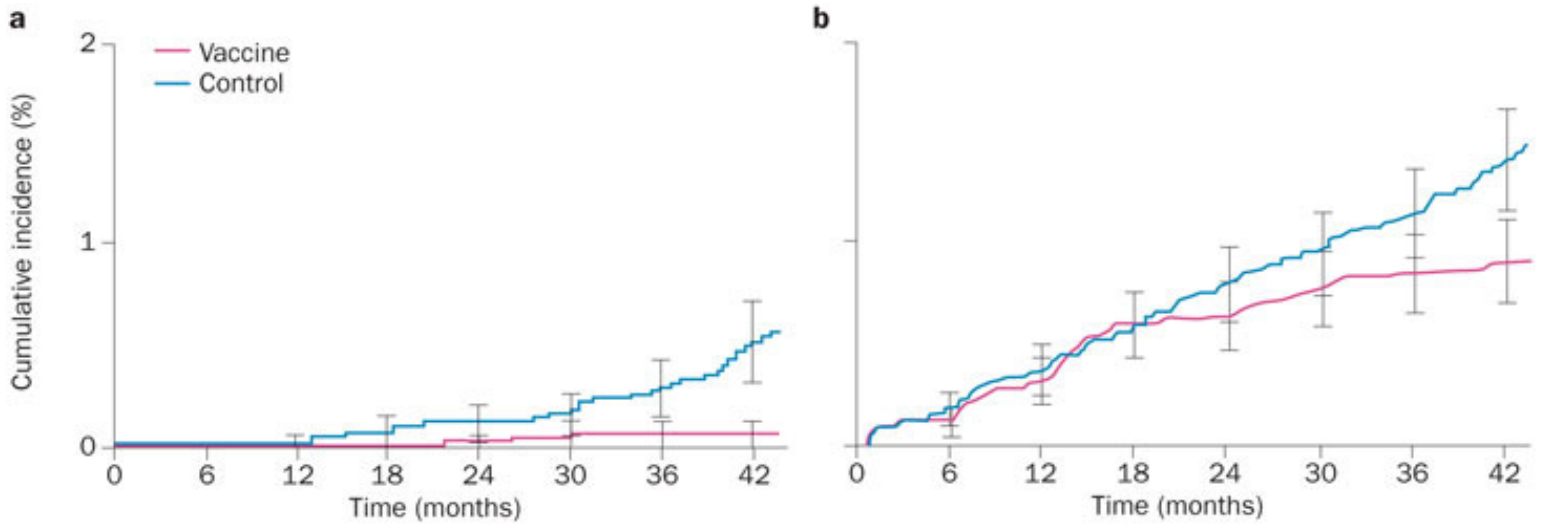
Markowitz *et al*, MMWR Recomm Rep. 2014;63(RR-05):1-30

Per-protocol efficacy of quadrivalent human papillomavirus vaccine for prevention of HPV 6-, 11-, 16-, and 18-related disease among males aged 16–26 years

Endpoint	Vaccine		Control		Vaccine efficacy
	No.	Cases	No.	Cases	%
Genital warts	1,397	3	1,408	28	89.4
PIN	1,397	0	1,408	3	100.0
AIN 1/2/3	194	5	208	24	77.5
AIN2/3	194	3	208	13	74.9

Markowitz *et al*, MMWR Recomm Rep. 2014;63(RR-05):1-30

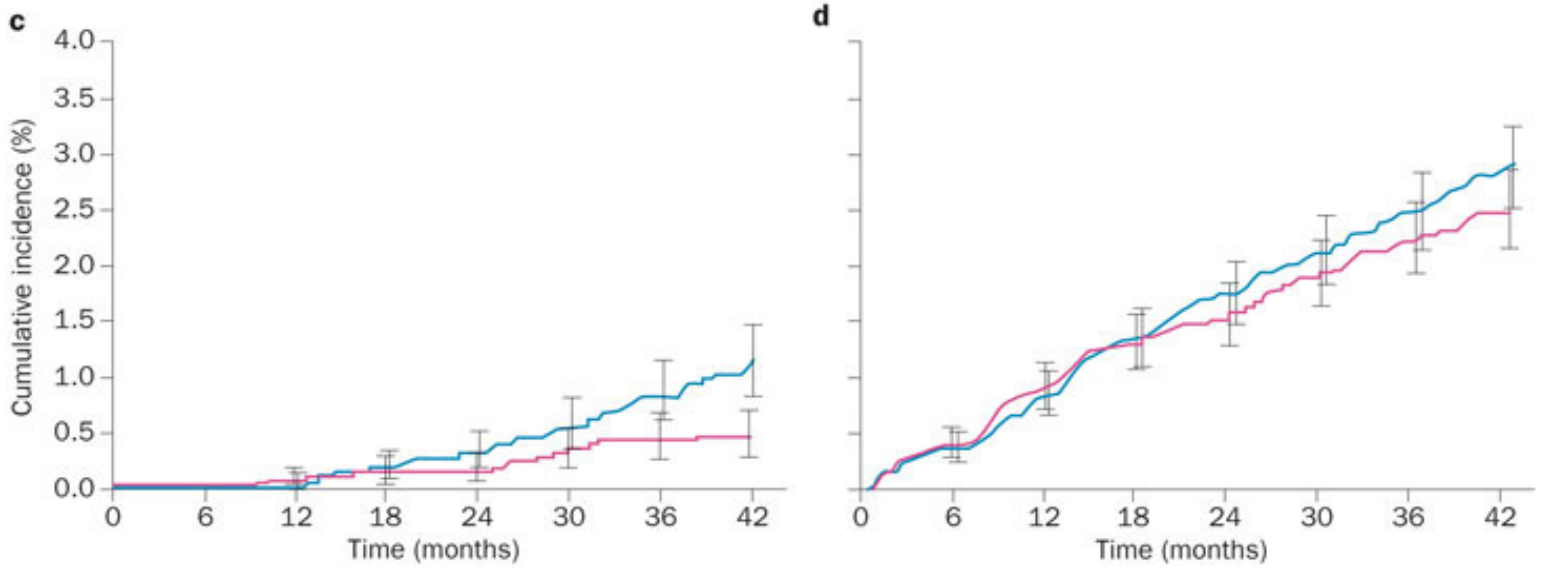
Kaplan–Meier curves of the estimated cumulative incidence of CIN3+ in the PATRICIA and FUTURE clinical trials



Number at risk																
Vaccine	5,466	5,463	5,401	5,322	5,237	5,136	4,931	4,764	8,694	8,663	8,516	8,329	8,178	8,013	7,684	7,412
Control	5,452	5,445	5,369	5,272	5,192	5,103	4,902	4,721	8,708	8,671	8,513	8,313	8,160	8,008	7,676	7,390

a) Women who were HPV PCR-negative at baseline and who received control or Cervarix® vaccines
b) The intention-to-treat cohort who received control or Cervarix® vaccines

Kaplan–Meier curves of the estimated cumulative incidence of CIN3+ in the PATRICIA and FUTURE clinical trials



Number at risk																
Vaccine	4,616	4,613	4,560	4,519	4,479	4,420	4,317	3,336	8,582	8,490	8,346	8,192	8,061	7,920	7,709	5,879
Control	4,680	4,675	4,627	4,580	4,523	4,402	4,349	3,372	8,598	8,523	8,355	8,203	8,060	7,912	7,671	5,866

c) Women who were HPV6, HPV11, HPV16 and HPV18 PCR-negative at baseline and who received control or Gardasil® vaccines

d) The intention-to-treat cohort who received control or Gardasil® vaccines. All data points have 95% CI error bars marked

Lehtinen *et al,* Nature Reviews Clinical Oncology 2013, 10:400-410

Efficacy and safety of HPV vaccination

- 100% sero-conversion
- Sero-positivity remains > 98% at 9 years
- 100% protection of CIN 2/3 caused by HPV 16/18 for at least 6 years in HPV-naïve populations
- Some cross protection against CIN 2/3 caused by HPV 45 and HPV 31
- Vaccine-induced antibody levels maintained over 9 years (both vaccines) robust recall response (quadrivalent)
- Safe and well-tolerated

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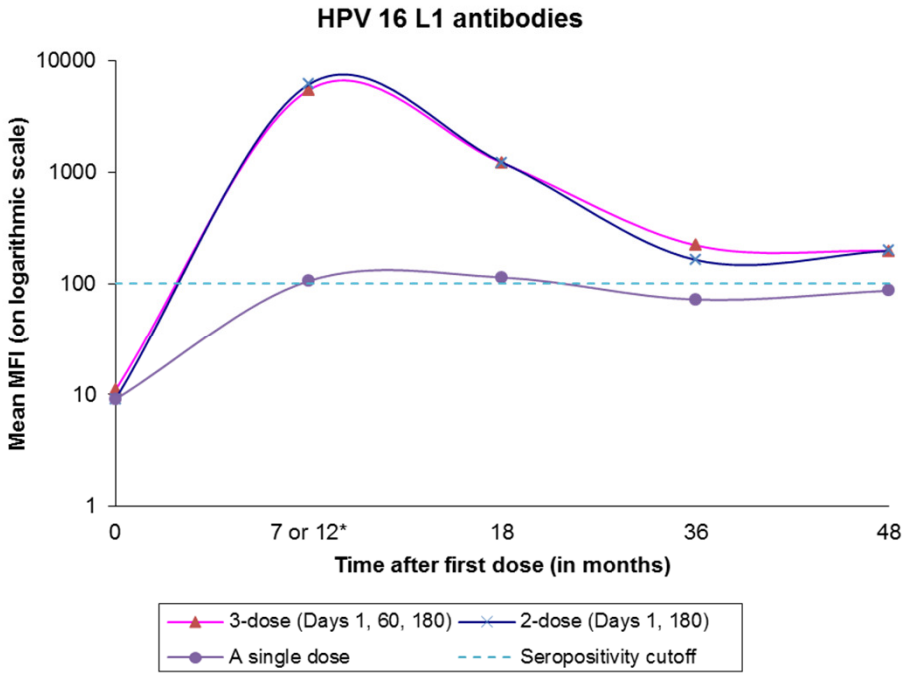
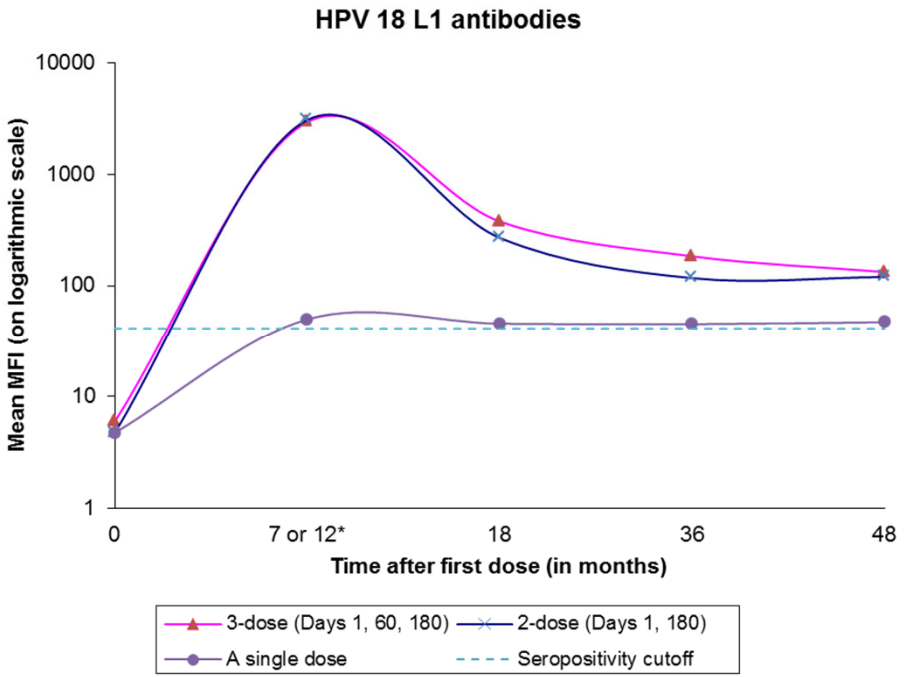
Randomised Trial of 2 versus 3 doses of HPV vaccination in India

Mean MFI values for HPV 16, 18 L1 antibodies at different time points among girls who completed vaccination per protocol (vaccination at day 1, 60 and 180 (3-dose group)
or day 1 and 180 (2-dose group)), and those who did not have their complete vaccine schedules (vaccination at day 1 and 60 or a single dose)





Sankaranarayanan *et al.*, Lancet Oncol. 2016;17(1):67-77

Supported by the Bill & Melinda Gates Foundation
Vaccines provided by Merck

FIGO
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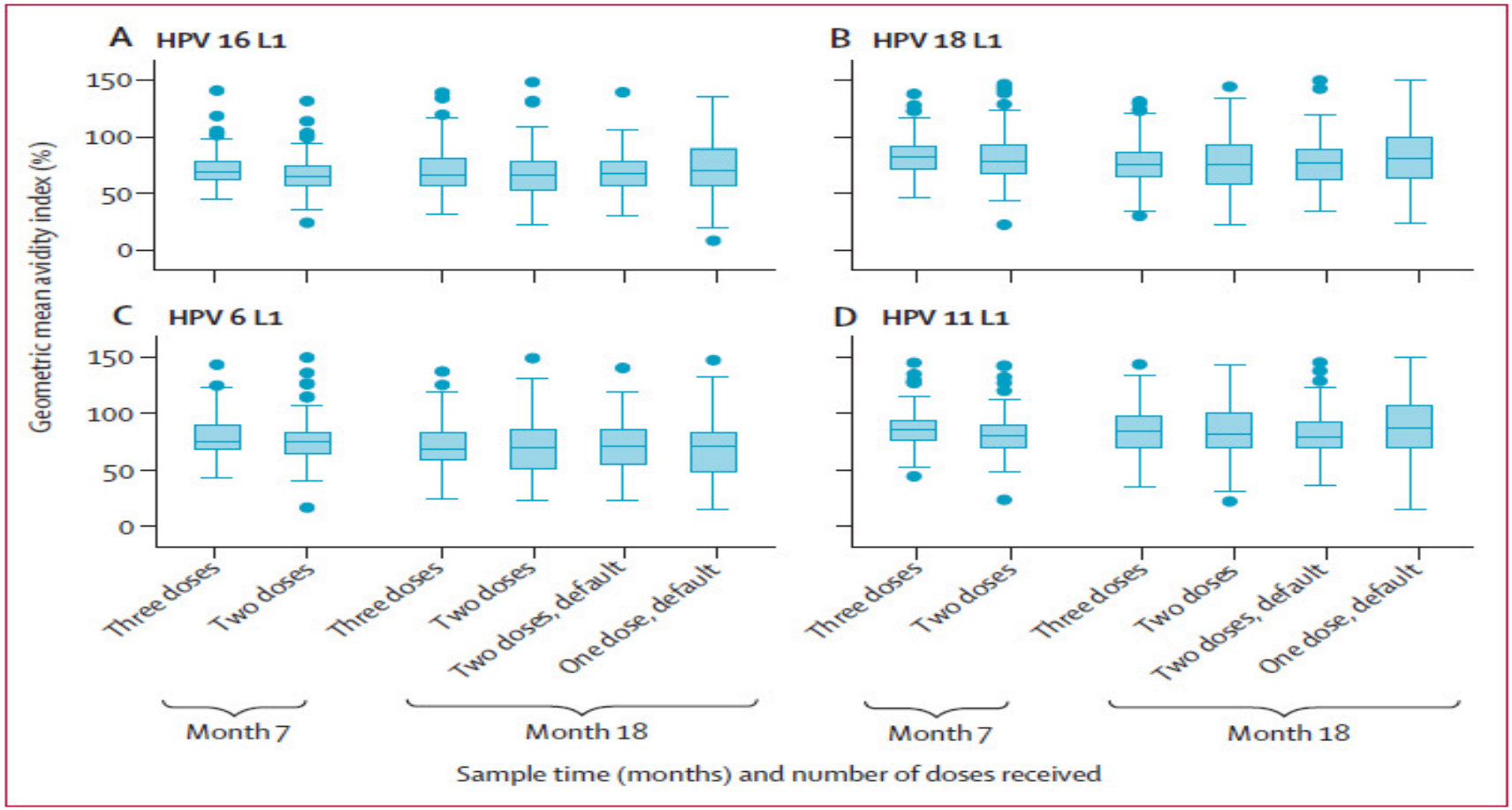
Randomised Trial of 2 versus 3 doses of HPV vaccination in India

Geometric mean MFI avidity index of *HPV 16, 18, 6 and 11 L1* antibodies

at 18 months after the first dose among girls who received vaccination per protocol, and those who did not have their complete vaccine schedules



Sankaranarayanan *et al.*, Lancet Oncol. 2016;17(1):67-77

Supported by the Bill & Melinda Gates Foundation

Vaccines provided by Merck

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Evaluation of less than 3 doses of HPV Vaccination in India:
Frequency of persistent HPV 16 and 18 infection in 1235 vaccinated women by dose regime and 738 unvaccinated women

- 3-Dose: 0/241
- 2-Dose (day 1-180): 0/224
- 2-Dose (day 1-60) : 0/365
- 1-Dose: 0/405
- All vaccinated girls: 0/1235
- UNVACCINATED WOMEN: 6/738 (0.8%)

Sankaranarayanan *et al.*, Lancet Oncol. 2016;17(1):67-77

Supported by the Bill & Melinda Gates Foundation

Vaccines provided by Merck

HPV vaccine efficacy of fewer than 3-doses in preventing HPV infections in Costa Rica

Doses	Arm	Women No	Women with HPV infections (%)	HPV vaccine efficacy
3 doses	Control	3010	133 (4.4%)	
	HPV	2957	25 (0.9%)	80.9%
2 doses	Control	380	17 (4.5%)	
	HPV	422	3 (0.7%)	84.1%
1 dose	Control	188	10 (5.3%)	
	HPV	196	0	100%

Kreimer A *et al*, JNCI 2011;103:1-8

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WHO's Strategic Advisory Group of Experts (SAGE) on 2-dose and 3-dose HPV vaccination, February 2014

- SAGE recommends 2-dose vaccination, 6-months or 1-year apart between the two doses, if vaccination is initiated prior to 15 years of age,
- 3-dose schedule is necessary if vaccination is initiated after 15th birth day.
- 3-dose schedule is recommended for immuno-comprised individuals, including HIV infected persons.

http://www.who.in/immunization/sage/meetings/2014/april/report_summary_april_2014/en

HPV vaccine safety

- The GACVS has systematically investigated HPV vaccine safety concerns
- To date, GACVS has not found any safety issue that would alter its recommendations

Global Advisory Committee on Vaccine Safety, 2-3 December 2015. Wkly Epidemiol Rec. 2016 Jan 22;91(3):21-31.

FIGO
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HPV vaccine safety

- More than 250 million doses of HPV vaccines have been administered since 2007
- No serious adverse event has been directly linked to HPV vaccination
- The frequency of anaphylaxis ~ 1/200,000 doses (similar to other vaccines)

FIGO
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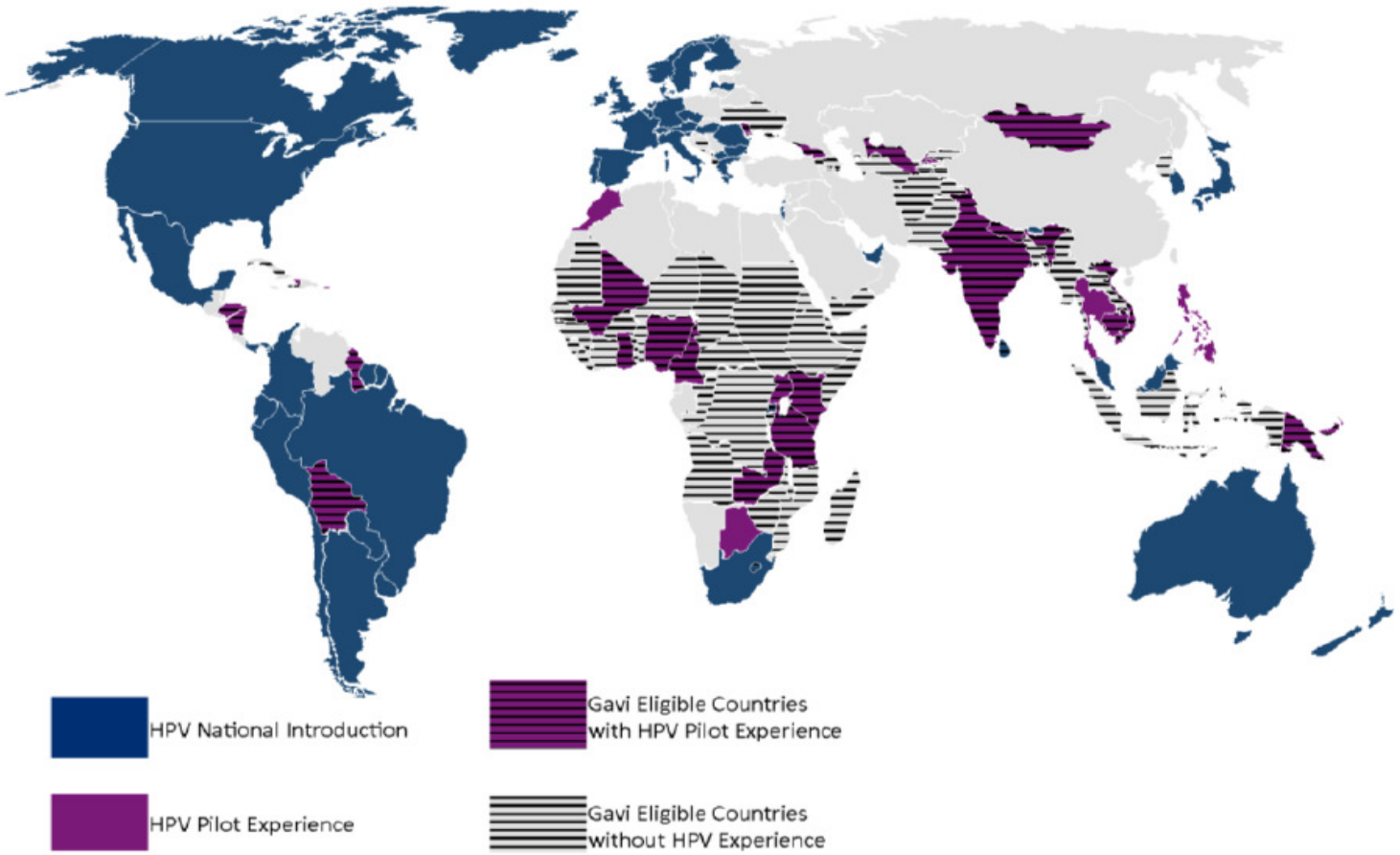
Global map showing HPV vaccination experience in Gavi eligible and non-eligible countries



Hanson *et al.*, Vaccine. 2015;3:408-419

HPV vaccination as part of National immunization programs

- HPV vaccination as part of National Immunization Programs (NIP) or pilot demonstration programs in **83 countries**
- Australia, UK, USA and Canada were the among the first countries to implement HPV vaccination
- In Europe, the countries implementing HPV vaccination as part of NIP increased from 3 in 2007 to 29 in 2015
- **Bhutan, Panama and Rwanda** were among the first LMICs to implement HPV vaccination in NIP

Markowitz et al., Vaccine. 2012;30 Suppl 5:F139-48,Sankaranarayanan. Int J Gynaecol Obstet. 2015;131 Suppl 1:S33-5,Herrero et al.Lancet Oncol. 2015;16(5):e206-16,Sankaranarayanan et al., Womens Health. 2015;11(2):201-12,Hansen et al., Vaccines (Basel) 2015; 3: 408-19

Bhutan: pilot program followed by national scale-up

- Pilot phase (Oct 2009-Apr 2010)
  - ACCF/GAP program donation of 9,600 doses
  - School-based (22), 3,167 girls aged 11-13 years targeted
  - 94% 3rd dose coverage
- National scale-up (May-Nov 2010)
  - GAP donation of 184,000 doses
  - Schools, 47,888 girls 12-18 year old eligible
  - 96% 3rd dose coverage
- National program (2011)
  - Health clinics based delivery, 12 year old (2012,2013) (3rd dose coverage 69%)
  - **School based delivery (2014), 90% 3rd dose coverage**
- The Bhutan HPV vaccine program is a model for other developing countries that aspire to implement national HPV vaccination programs

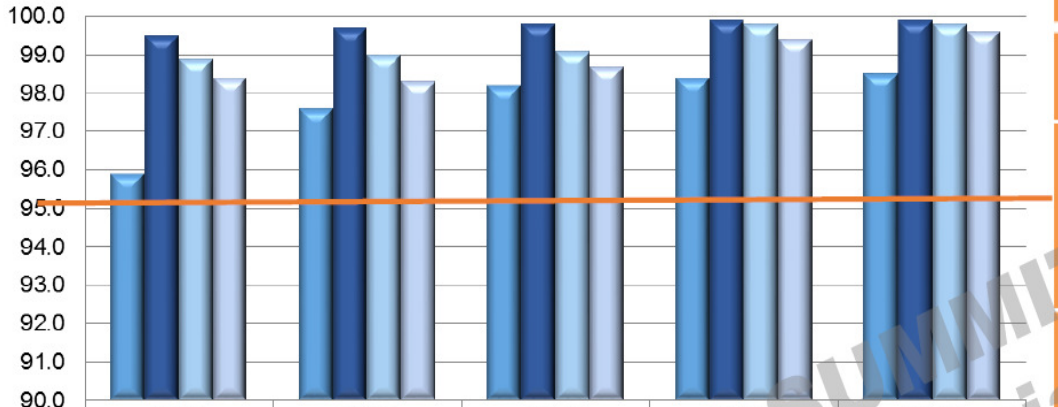
Dorji *et al.*, Vaccine. 2015;33(31):3726-30

HPV vaccination programme in Malaysia

- Introduced in mid-2010
- Primarily school-based delivery
  - community health centres for missed girls or out-of-school girls
- Extensive communications preparation: electronic media, radio, newspapers, posters, pamphlets
- Strong monitoring system
- HPV vaccination well accepted by communities and parents
- Eligible population: 236,000 (13 year old girls)

Malaysia HPV vaccination performance 2010 - 2014

Program target: 3 doses completion at 95%

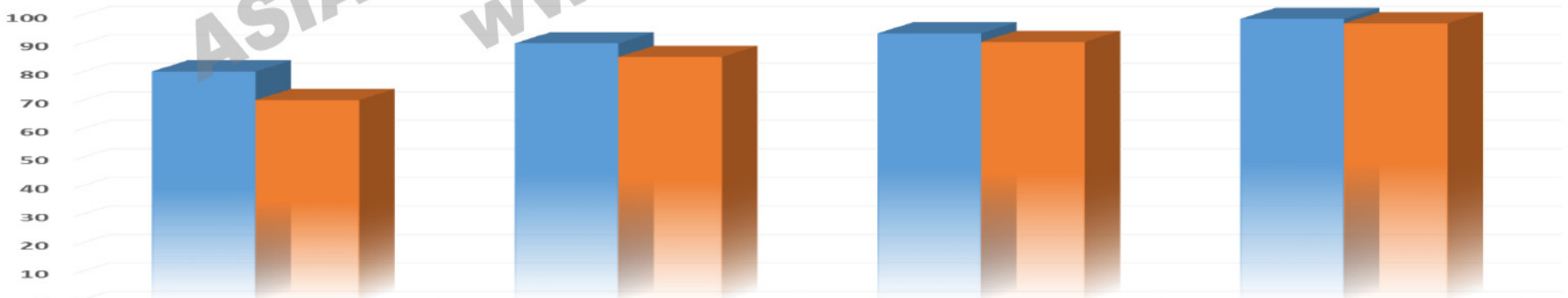


	2010	2011	2012	2013	2014
Acceptance	95.9	97.6	98.2	98.4	98.5
Dose 1	99.5	99.7	99.8	99.9	99.9
Dose 2	98.9	99.0	99.1	99.8	99.8
Completed 3 doses	98.4	98.3	98.7	99.4	99.6

AEFI REPORTED TO PHARMACEUTICAL BUREAU BETWEEN 2010 AND 2014

YEAR	2010	2011	2012	2013
Total doses of vaccine delivered	687,735	678,897	693,905	727,518
Number AEFI report recieved	403	3023	1757	960
	0.06%	0.45 %	0.25 %	0.13%

NATIONAL HPV SCHOOL BASED HPV VACCINATION PERFORMANCE FOR 12 - 13 YEARS OLD GIRLS : AUSTRALIA, ENGLAND, SCOTLAND AND MALAYSIA SCORE CARD



	AUSTRALIA (12 -13), 2011	ENGLAND (12 -13), 2012/13	SCOTLAND (12-13), 2008/09	MALAYSIA (12-13) 2010
Dose 1	81	90.9	94.4	99.5
Dose 3	71	86.1	91.4	97.9

Courtesy slide from : Saidatul Norbaya Buang and Rohani Jahis for Asia Dengue Summit

HPV vaccination coverage in Rwanda, 2011

Coverage	Dose 1	Dose 2	Dose 3
Girls vaccinated in school (No.)	91 752	89 704	88 927
Girls vaccinated outside school (No.)	2 136	3 066	3 180
Total number of girls vaccinated (No.)	93 888	92 770	92 107
Cumulative coverage	**95%**	**94%**	**93%**

Binagwaho *et al.*, Bull World Health Organ. 2012;90(8):623-8

National HPV vaccination program in Panama

- Initiated in 2008
- Delivered in schools and clinics for 10 year old girls
- In 2009, 1 dose coverage was 89% and 3-dose coverage was 46%
- In 2010, 3-dose coverage was 67%
- In 2011, 3-dose coverage improved to 81%

Impact of HPV vaccination in real world settings

- Over the last decade, impact of HPV vaccination in real-world settings is increasingly evident, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake
- Maximal reductions of ~90% for HPV 6/11/16/18 infection, ~90% for genital warts, ~60% for low-grade cytological cervical abnormalities, and ~90% for high-grade histologically-proven cervical abnormalities have been reported
- The full public health potential of HPV vaccination not yet realized. HPV-related disease remains a significant source of morbidity and mortality in developing and developed nations, underscoring need for HPV vaccination programs with high coverage.

Garland *et al.*, Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]

Global impact of HPV vaccination and herd effects

- A pooled analysis of 20 studies in 9 high income countries with >50% coverage
- 140 million person years of follow-up
- HPV16 and HPV 18 infections declined by 68% (RR 0.32, 95% CI: 0.19-0.52)in girls aged 13-19 years
- Anogenital warts declined by 61% (RR: 0.39, 95% CI: 0.22-0.71) in 13-19 year old girls
- HPV types 31,33, 45 declined by 28% (RR: 0.72, 95% CI:0.54-0.96)
- Anogenital warts declined by 34% (RR: 0.66, 95% CI: 0.47-0.91) in boys <20 years age
- Anogenital warts declined by 32% (RR: 0.68, 95% CI: 0.51-0.89) in women <30 years age

Drolet *et al.,* Lancet Infect Dis. 2015;15:565-80

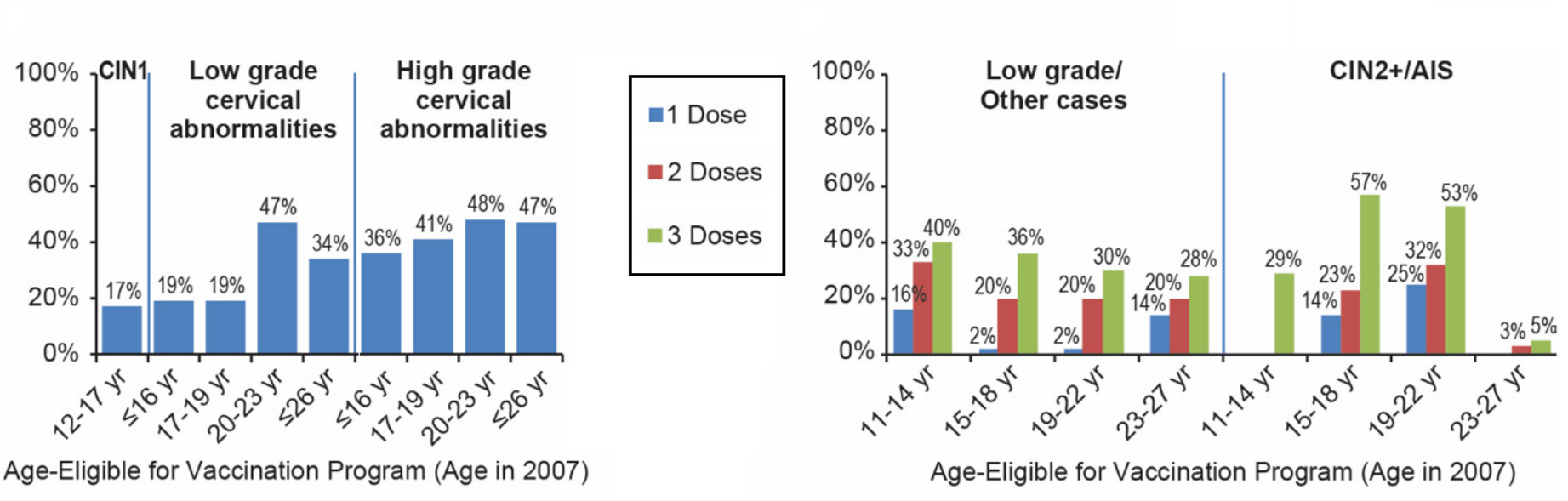
Global impact of HPV vaccination and herd effects in countries with <50% coverage

- HPV16 and HPV 18 infections declined by 50% (RR 0.50, 95% CI: 0.34-0.74) in girls aged 13-19 years
- Anogenital warts declined by 14% (RR: 0.86, 95% CI: 0.79-0.94) in 13-19 year old girls
- No indication of cross-protection or herd effects
- Long-term population-level effects of HPV vaccination programmes are promising
- Continued monitoring is essential to identify any waning efficacy or type-replacement.

Drolet *et al.,* Lancet Infect Dis. 2015;15:565-80

Impact and effectiveness of HPV vaccination on cervical cytological and histological abnormalities

Australia: Victoria



Australia: Queensland

Garland *et al.*, Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]

Impact and effectiveness of HPV vaccination on cervical cytological and histological abnormalities

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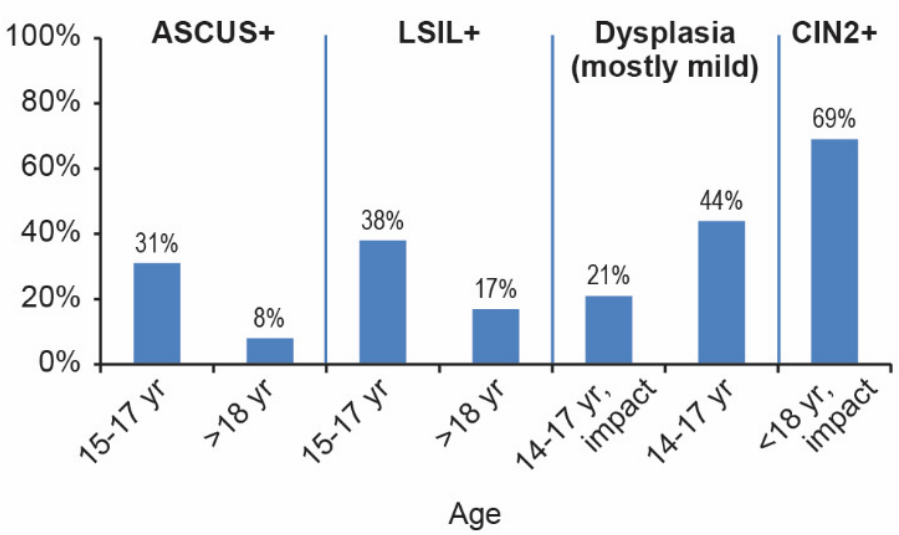
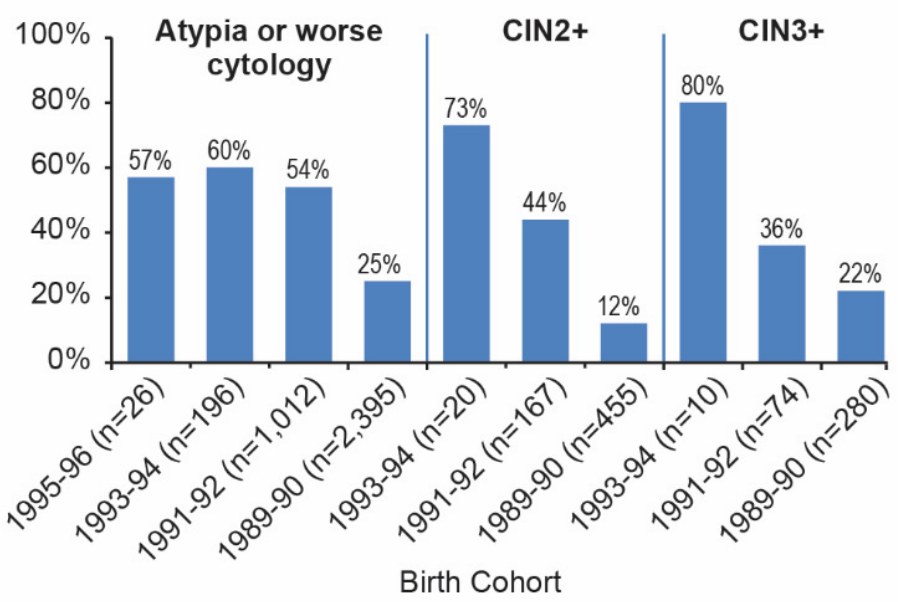
Canada



Denmark

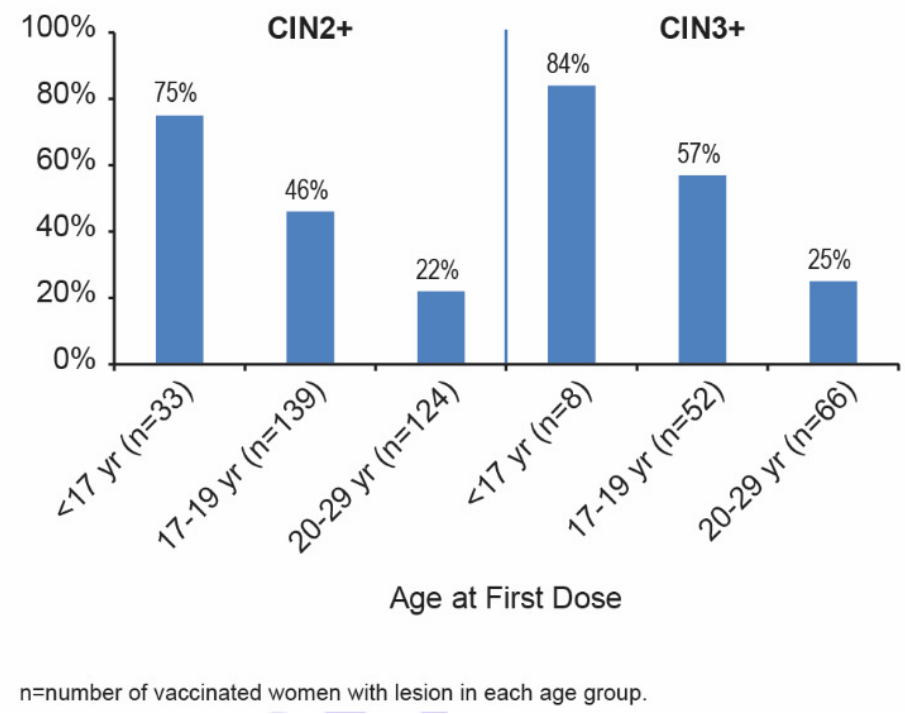


n=number of women with lesion in each age group, vaccinated and unvaccinated included.

Garland *et al.*, Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]

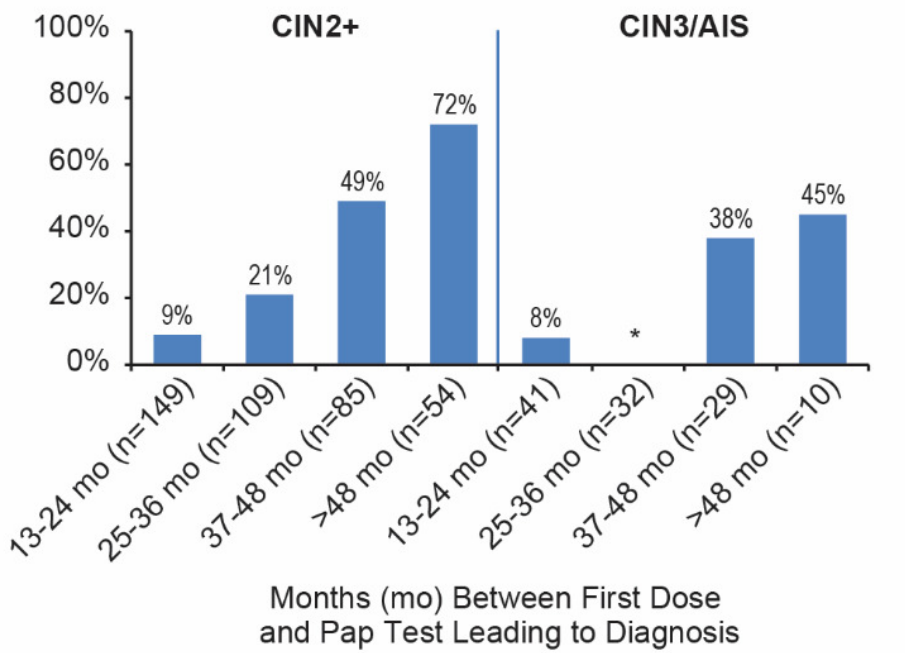
Impact and effectiveness of HPV vaccination on cervical cytological and histological abnormalities

Sweden



n=number of vaccinated women with lesion in each age group.

United States



n=number of vaccinated women with lesion in each time category.

Garland *et al.*, Clin Infect Dis. 2016. pii: ciw354. [Epub ahead of print]

HPV vaccine
Notes & Theories

We know it's effective. So why is there opposition to the HPV vaccine ?

David Robert Grimes

Over 90% of cervical cancers are caused by HPV. But squeamishness about sex and unsupported safety fears are threatening vaccination programmes

Monday 11 January 2016 16.44 GMT

The HPV vaccine Gardasil is at least 99% effective against the four most odious HPV subtypes in young women.

https://www.theguardian.com/science/blog/2016/jan/11/why-is-there-opposition-hpv-vaccine-cervical-cancer

Slides prepared by

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On behalf of the

FIGO Committee on Gynecologic Oncology